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The Cancer Genome Atlas (TCGA): Breast and Ovarian Cancers

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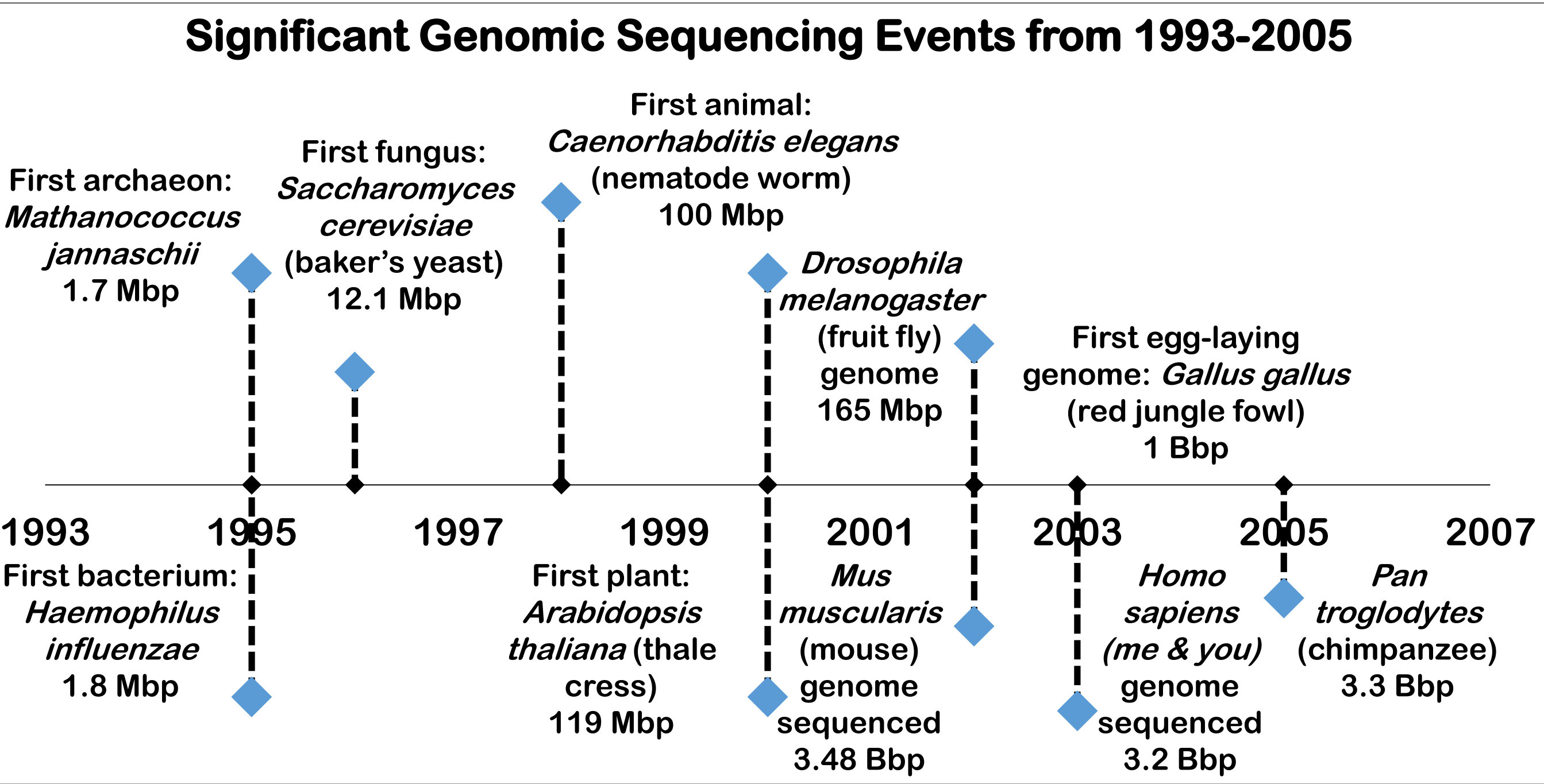
The Cancer Genome Atlas (TCGA): Breast and Ovarian Cancers

Laura Ann Riccio

Faculty Sponsor: Dr. Niall G. Howlett

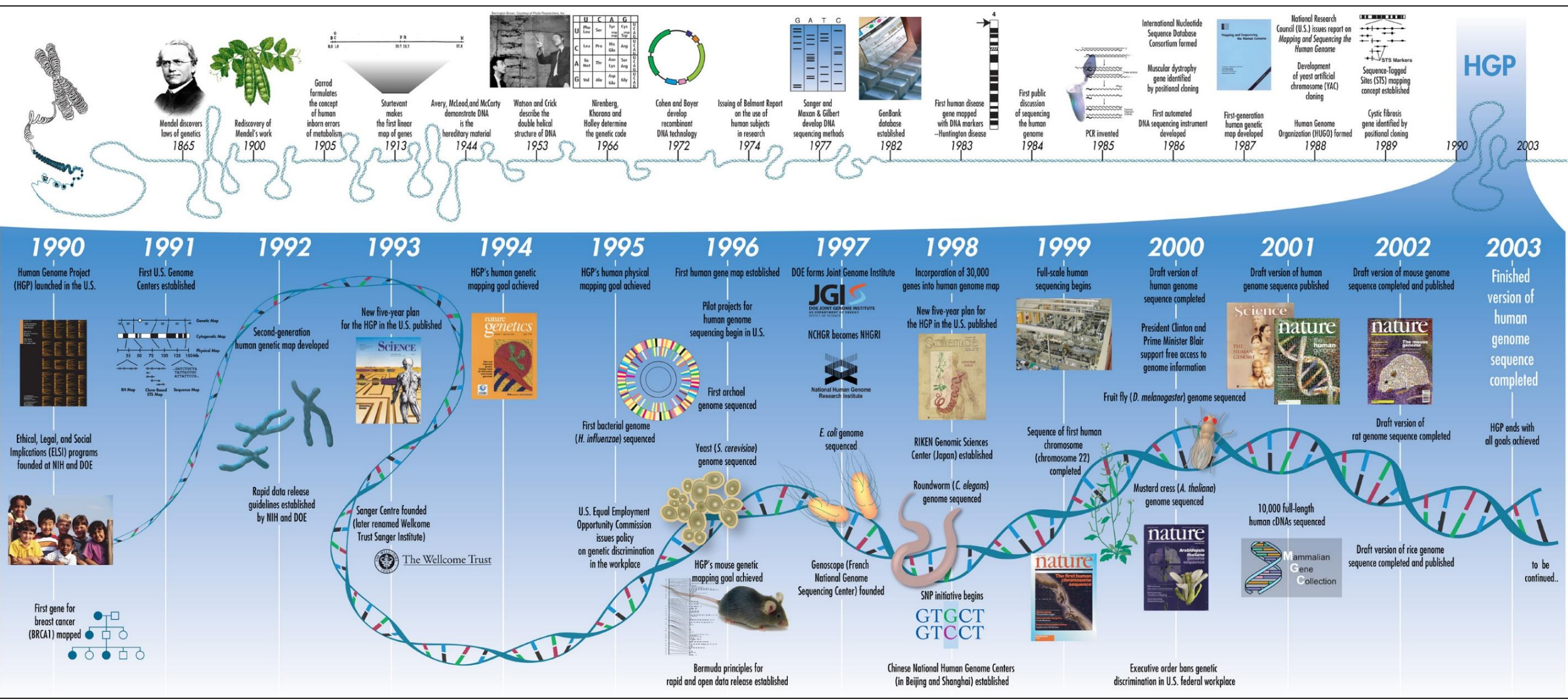
Introduction to Genomics

A genome is the complete ordered sequence of DNA bases (A, C, G, T) which make up all of the protein- and RNA-coding genes, and regulatory sequences necessary for the construction of an organism. The field of genomics began in the 1970's when Walter Fiers and his team in Ghent, Belgium sequenced the genome of the M2 bacteriophage.



Human Genome Project

HGP was an international, collaborative research program with the goal to sequence and map the full human genome of 3 billion base pairs to gain a better understanding of all of the genes that are present. It was initiated in 1990 and a draft sequence was published in 2003, paving the way for the development of new genomics-based research projects.

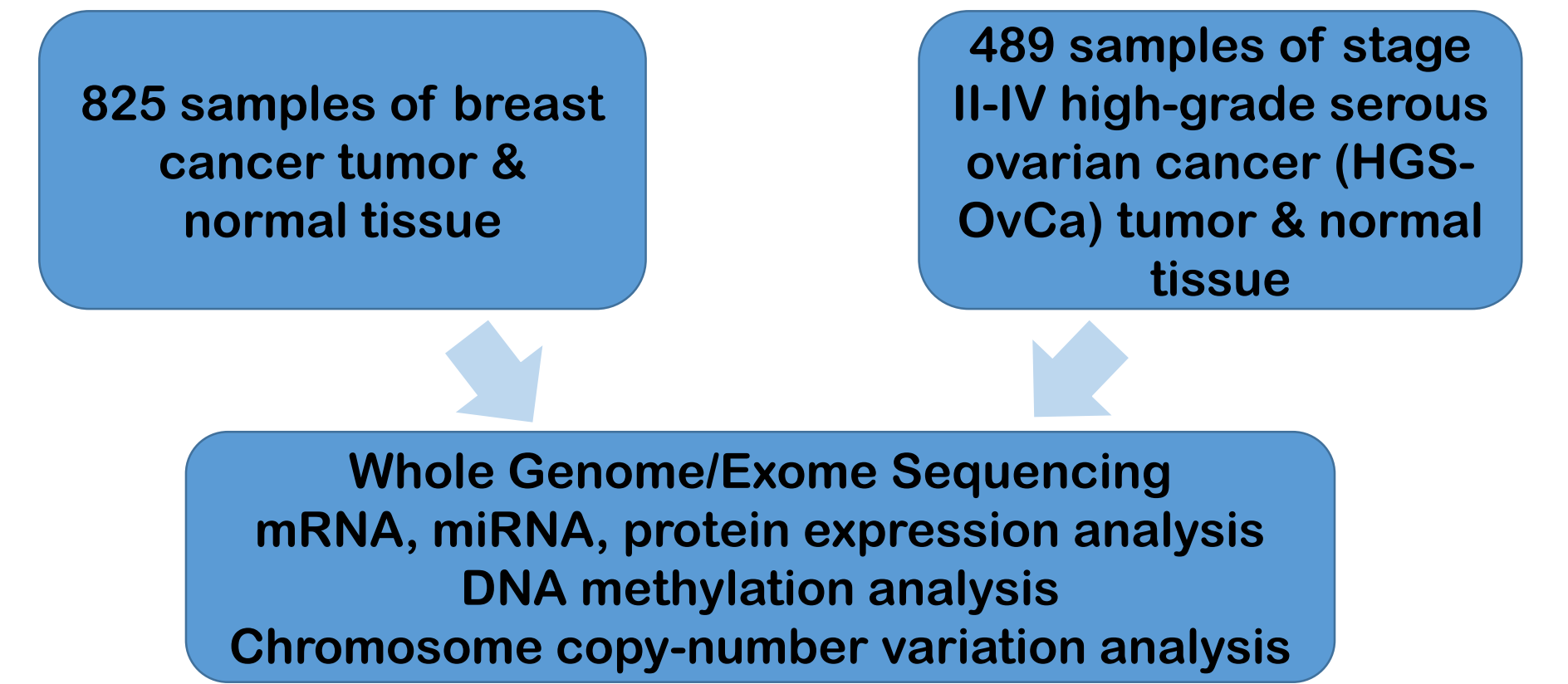


The Cancer Genome Atlas

The National Institutes of Health (NIH) and the National Human Genome Research Institute (NHGRI) initiated a pilot project called The Cancer Genome Atlas (TCGA) in 2006. The overall goal of TCGA is to catalog all of the significant genomic changes in the major types and subtypes of cancer. It is hoped that this catalog of information will serve as a critical resource for the prevention, diagnosis, and treatment of these cancers.

Key. Estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) are cell surface proteins that bind to hormones such as estrogen and epidermal growth factor, respectively, in tissues such as the uterus and breast. Progesterone receptor (PR) is a protein found in the cytoplasm of breast epithelial cells, that binds to the hormone progesterone. These proteins regulate cell division and proliferation.

TCGA Breast & Ovarian Cancers



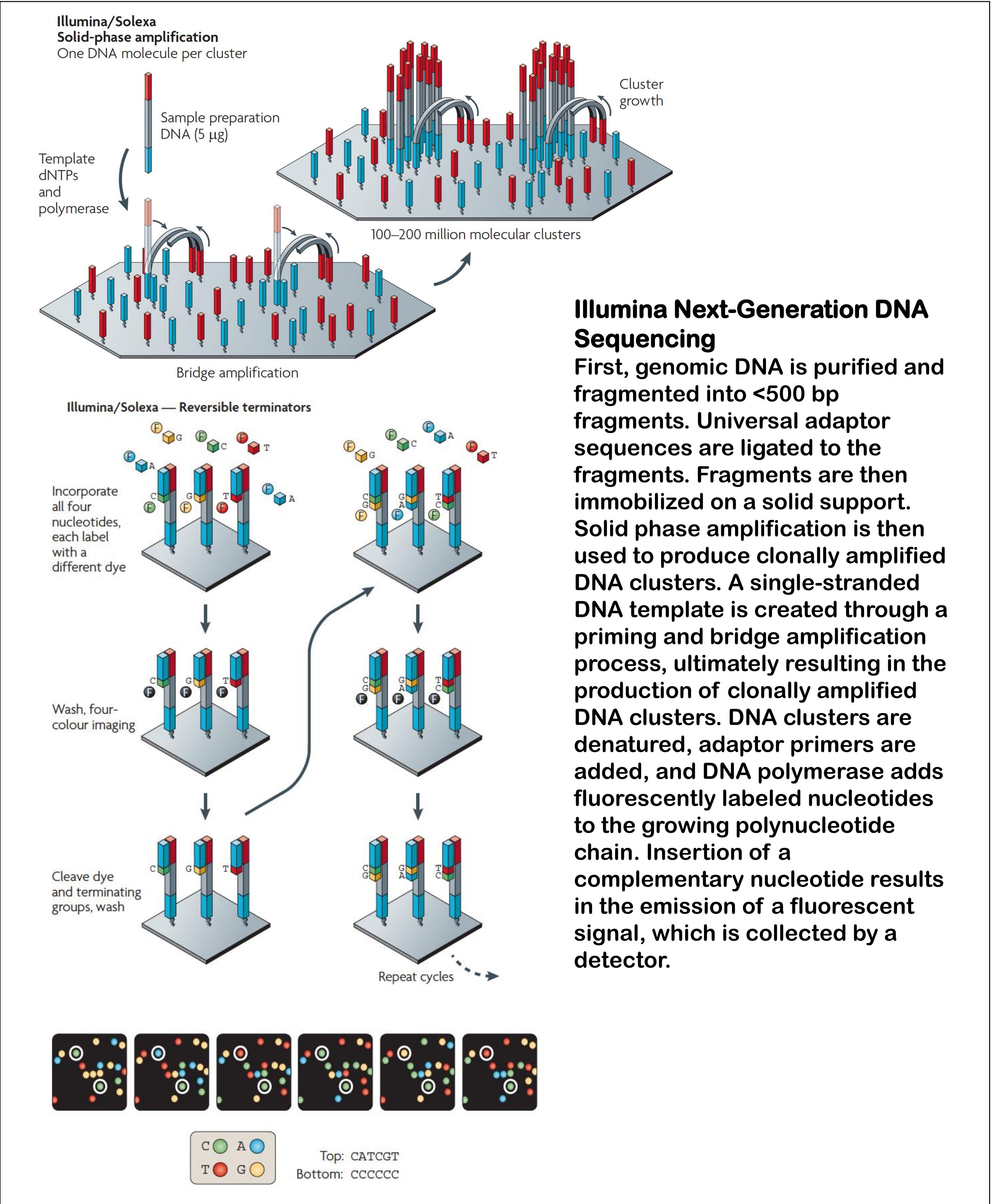
Genes Mutated in HGS-OvCa			
Genes	Type of Mutation(s)	No. of Mutated Samples	Percent of Mutations
<i>TP53</i>	Missense	302	96%
<i>RB1</i>	Missense	6	2%
<i>NF1</i>	Missense	13	4%
<i>BRCA1</i>	Germline, somatic	11	3%
<i>CSMD3</i>	Missense	19	6%
<i>CDK12</i>	Nonsense, indel, missense	9	3%
<i>FAT3</i>	Missense	19	6%
<i>GABRA6</i>	Missense	6	2%
<i>BRCA2</i>	Germline, somatic	10	3%

Genes Mutated in Breast Cancer mRNA Subtypes				
Genes	Luminal A (n=225)	Luminal B (n=126)	HER2-enriched (n=57)	Basal-like (n=93)
<i>PIK3CA</i>	45%	29%	39%	9%
<i>MAP3K1</i>	13%	5%	4%	0%
<i>GATA3</i>	14%	15%	2%	2%
<i>TP53</i>	12%	29%	72%	80%
<i>CDH1</i>	9%	5%	5%	0%
<i>MAP2K4</i>	7%	2%	2%	0%
<i>PTEN</i>	4%	4%	2%	1%
<i>AKT1</i>	4%	2%	2%	0%
<i>RB1</i>	0.4%	3%	0%	4%
<i>MLL3</i>	8%	6%	7%	5%
<i>TBX3</i>	3%	4%	0%	1%
<i>RUNX1</i>	5%	2%	4%	0%
<i>CBFB</i>	2%	2%	2%	0%
<i>AFF2</i>	1%	2%	5%	4%
<i>PIK3R1</i>	0.4%	2%	4%	0%
<i>PTPN22</i>	0.4%	2%	5%	0%
<i>PTPRD</i>	2%	4%	4%	1%
<i>NF1</i>	2%	4%	0%	2%
<i>CTCF</i>	4%	2%	2%	1%
<i>FOXA1</i>	2%	2%	2%	0%
<i>SF3B1</i>	3%	0%	4%	1%
<i>NCOR1</i>	5%	2%	0%	2%
<i>CDKN1B</i>	1%	1%	2%	0%

Luminal A	Luminal B	HER2E	Basal-like
■ ER+	■ ER+	■ ER-	■ ER-
■ PR+	■ PR+	■ PR-	■ PR-
■ HER2-	■ HER2+	■ HER2+	■ HER2-

Next-Generation Sequencing

The Illumina next-generation sequencing platform was used for both high-grade serous ovarian cancer (HGS-OvCa) and breast cancer. It uses a sequencing by synthesis (SBB) technology which incorporates four fluorescently-labeled nucleotides to sequence DNA clusters.



What Has Evolved From This?

One of the most significant findings from TCGA was that basal-like breast cancer subtype is most similar to HGS-OvCa, containing similar types and frequencies of mutations. These results suggest that the two cancers may have a similar molecular origin, and may be responsive to similar therapies.

Predominant similarities:

- High frequency of *TP53* mutations
- Inactivation of *BRCA1*
- Amplification and high expression of *cMYC*
- Loss of *RB1*

References

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Michael L. Metzker (2010) *Nature Rev. Genet.* 11: 31-46.
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